HEMAGGLUTININ-SPECIFIC ANTIBODIES AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to hemagglutinin-specific antibodies, fragments thereof, and uses thereof. More specifically, the present invention relates to hemagglutinin-specific antibodies and fragments thereof able to recognize antigen from multiple influenza strains.

BACKGROUND OF THE INVENTION

[0002] Influenza is an infectious disease caused by the influenza virus which belongs to the Orthomyxoviridae family. Based on their core proteins, influenza viruses are classified into types A, B, and C. The two main types of influenza virus responsible for seasonal flu epidemics are types A and B. Influenza A virus can be further characterized by serotype based on the hemagglutinin (HA) and neuraminidase (NA) proteins on the viral surface. Currently, there are 18 known subtypes of HA and 11 subtypes of NA. Based on HA subtypes, influenza A viruses are further divided into two phylogenetic groups: group 1 (H1, H2, H5, H6, H8, H9, H11, H12, H13, H16, H17 and H18) and group 2 (H3, H4, H7, H10, H14 and H15). Point mutations in the viral genome RNA of a given HA subtype already in circulation, or a new subtype of HA that arises through antigenic shift (Kang et al., 2011) can result in an influenza pandemic.

[0003] According to the World Health Organization (WHO), the influenza virus is responsible for up to 500,000 deaths per year worldwide. In order to combat the potential fatal effect of influenza virus, vaccines are produced yearly and administered to global populations. However, there are thousands of influenza virus strains. Presently, each strain requires a specific antibody for detection and quantification of HA, the most abundant protein expressed at the surface of the virus. Regulatory agencies such as the WHO are responsible for producing and distributing the antibodies used to quantify new vaccine lots throughout the world. Antibody production can take from 3 up to 16 weeks, which causes significant delays for the vaccine industry.

[0004] Generally, quantification of new vaccine lots is the bottleneck in vaccine distribution. Quantification of HA is currently performed using an assay called the Single Radial Immunodiffusion (SRID) assay. However, this assay is lengthy, laborious, and highly variable depending on the operator. In addition, standardised reagents necessary for SRID (polyclonal sera and antigen), need to be updated every year, which takes 12-16 weeks and is reliant on obtaining purified HA antigen. While the SRID assay is the only quantification method that is officially accepted by regulatory agencies, alternative quantification methods such as Enzyme-Linked Immunosorbent Assays (ELISA) could be more efficient.

[0005] Currently, specific antibodies against each strain are generated by injecting animals with isolates from each strain. However, the use of strain-specific antibodies can cause delays in releasing new vaccine lots. Using antibodies with broad specificity can speed up the detection and quantification of new influenza strains. To date, only two pan-HA antibodies are able to recognize all 3 groups of influenza commonly circulating in humans (type A group 1, type A group 2, and type B).

[0006] CR9114 is a human monoclonal antibody that was isolated using combinatorial display library derived from human B cells of subjects exposed to influenza (Dreyfus et al, 2012). CR9114 was shown to detect 10 influenza B viruses, as well as five HA belonging to influenza A (three from group 1 and two from group 2), but was not tested against all subtypes. However, its ability to recognize all HA subtypes remains untested.

[0007] Uni-1 was raised at Health Canada against a peptide sequence that is known to be highly conserved among influenza strains: GLFGAIAGFIEGGW (SEQ ID NO:29). The peptide sequence was derived from the HA fusion peptide, which was selected using bioinformatics analyses. Notably, Uni-1 was able to detect 13 different HA subtypes (H1 to H13) as well as B/Malaysia/2506/2004 by western blot (Chun et al, 2008).

[0008] Unfortunately, the main constraint with Uni-1 is that the antibodies are polyclonal rabbit antibodies, which result in high lot to lot variations. Additionally, the peptide used to raise Uni-1 was unable to elicit an immune response in mice, which has prevented production of monoclonal antibodies.

[0009] Thus, while some success has been achieved in the influenza field to generate antibodies with broad specificity to influenza HA, it is limited and not without drawbacks. The influenza community continues to seek faster and more accurate quantification methods to improve or replace the SRID assay, which could speed up the vaccine production and delivery system.

SUMMARY OF THE INVENTION

[0010] The present invention relates to hemagglutinin-specific antibodies, fragments thereof, and uses thereof. More specifically, the present invention relates to hemagglutinin-specific antibodies and fragments thereof able to recognize antigen from multiple influenza strains.

[0011] The present invention provides an isolated or purified antibody or fragment thereof, comprising:

[0012] a) a light chain comprising a complementarity determining region (CDR) L1 sequence of QSLLNSX$_1$X$_2$QKNX$_3$ (SEQ ID NO:1) where X$_1$=R or D, X$_2$=N or T, X$_3$=H or F; a CDR L2 sequence of X$_1$AS (SEQ ID NO:35) where X$_1$=W or F; and a CDR L3 sequence of QQYYX$_1$X$_2$X$_3$X$_4$T (SEQ ID NO:2) where X$_1$=T or S, X$_2$=Y or I, X$_3$=P or no amino acid, X$_4$=R or L,

and

[0013] b) a heavy chain comprising a complementarity determining region (CDR) H1 sequence of GYX$_1$X$_2$TX$_3$DYY (SEQ ID NO:3) where X$_1$=S or T, X$_2$=I or F, X$_3$=S or no amino acid; a CDR H2 sequence selected from the group consisting of IGYDGX$_1$K (SEQ ID NO:4) where X$_1$=S or T, and IYPGNGHT (SEQ ID NO:5), and a CDR H3 sequence selected from the group consisting of TRDRANWD-DYFDY (SEQ ID NO:6) and AYDLFNY (SEQ ID NO:7).

[0014] In one non-limiting example, the isolated or purified antibody or fragment described above may comprise a CDR L1 that is selected from the group consisting of QSLLNSRNQKNH (SEQ ID NO:8) and QSLLNS-DTQKNF (SEQ ID NO:9).

[0015] In another non-limiting example, the isolated or purified antibody or fragment thereof as previously